Hypokalaemia

What is hypokalaemia?

Hypokalaemia is usually defined as a serum concentration of potassium <3.5 mmol/L. It can be classified as follows:[1]

- Mild - 3.1-3.5 mmol/L.
- Moderate - 2.5-3.0 mmol/L.
- Severe - <2.5 mmol/L.

It is probably the most common electrolyte abnormality affecting hospitalised patients. Most cases are mild but in 5% of cases the potassium level it is <3.0 mmol/L. Severe hypokalaemia is even rarer. Importantly, even mild hypokalaemia can increase the incidence of cardiac arrhythmias.

98% of potassium is found within cells (only 2% is extracellular) with intracellular concentrations between 150-160 mmol/L.[2] The ratio of intracellular to extracellular potassium concentration determines the cellular resting membrane potential and influences the function of excitable tissues such as nerves and muscles. Maintenance of this concentration gradient across membranes is achieved by the enzyme sodium-potassium adenosine triphosphatase (Na+/K+-ATPase) that pumps two potassium ions into the cell in exchange for three sodium ions pumped out.

Serum-potassium concentration relates both to the internal balance between intracellular and extracellular fluids and the external balance determining the total body potassium. This is achieved by the kidney, mainly under the control of the hormone aldosterone secreted by adrenal glands.

Hypokalaemia causes (aetiology)

Most cases are the result of either diuretic consumption or loss of gastrointestinal (GI) fluids through persistent vomiting, chronic diarrhoea or laxative abuse. With vomiting, the cause is not mainly direct loss of potassium but that of chloride causing high levels of aldosterone which inhibits potassium reabsorption from the kidney tubules.

Classification of hypokalaemia

Increased loss	Transcellular shift	Decreased intake of potassium	Miscellaneous
Via the kidney: Thiazide or loop diuretics (the most common cause) Renal tubular acidosis Hypomagnesaemia Hyperaldosteronism - eg, Conn's syndrome, renal artery stenosis, Cushing's disease Tubulo-interstitial renal disease due to Sjögren's syndrome or systemic lupus erythematosus Excess liquorice ingestion Activation of the renin-angiotensin system - eg, Bartter's syndrome or Gitelman's syndrome Via the GI tract: Diarrhoea Vomiting (bicarbonate diuresis) Intestinal fistulae Villous adenoma Pyloric stenosis Laxative abuse	Alkalosis - metabolic or respiratory Insulin and glucose administration Catecholamines and beta$_2$ sympathomimetics - eg, acute illness, salbutamol Toluene intoxication (glue sniffing) Calcium-channel blockers (rare) Hypokalaemic periodic paralysis [3] Chloroquine intoxication Hypothermia	Inadequate potassium replacement in intravenous (IV) fluids whilst nil by mouth Total parenteral nutrition (TPN) Malnutrition Anorexia nervosa Hypocaloric protein diets for rapid weight loss	Chronic alcoholism (multifactorial) Chronic peritoneal dialysis Plasmapheresis

Bowel preparation with oral sodium phosphate solution Via the skin: Burns Erythroderma Increased sweating - eg, exercising in a hot climate Increased loss in sweat - eg, cystic fibrosis			

The most common congenital cause of hypokalaemia is Gitelman's syndrome, associated with impaired renal tubular ion transport due to a mutation in the Na+/Cl- co-transporter gene.[4] Bartter's syndrome is closely related but presents in infancy with faltering growth and is due to a mutation in the Cl- channel gene.

How common is hypokalaemia? (Epidemiology)

Hypokalaemia is a common problem, particularly amongst certain subgroups of the population. For example, it was found in 1.96% of elderly patients treated with potassium-losing diuretics (greater than those elderly who were normotensive).[5] It was also found in 2.5% of the over-75s in a Swedish study (strongly associated with use of thiazides or combination diuretics)[6] , 20.6% of British adults receiving thiazides[7] and 19.7% of anorexics in an outpatient setting.[8] Where hypokalaemia is linked to medications, earlier studies may be associated with higher dosing and subsequent greater likelihood of low potassium levels. The maxim more recently supports using the lowest dose (for the shortest time) to achieve the desired outcome.

Risk of developing hypokalaemia is increased by concomitant illness, particularly heart failure, alcoholism and nephrotic syndrome.

Hypokalaemia symptoms and presentation

- Mild forms are generally asymptomatic.

- In more severe conditions (ie potassium <3.0 mmol/L), symptoms include:
    - Lassitude.
    - Generalised weakness and muscle pain.
    - Constipation.
- At potassium <2.5 mmol/L, serious neuromuscular problems emerge, including:
    - Severe muscle weakness and paralysis (beginning in the lower extremities, progressing to the upper extremities and torso).
    - Respiratory failure (due to involvement of respiratory muscles).
    - Ileus (due to involvement of GI muscles).
    - Paraesthesia.
    - Tetany.
- Suspect the cause from clinical context - eg, diuretics, copious vomiting, prolonged diarrhoea. The patient may conceal their abuse of diuretics or laxatives and self-induced vomiting.
- Gitelman's syndrome typically presents early in adulthood with hypotension, alkalosis and salt wasting, together with hypomagnesaemia, hypocalciuria and hypermagnesuria. Clinical signs include salt craving, cramps, muscle weakness and aches, fatigue, generalised weakness and dizziness, nocturia and polydipsia.
- Incidental finding.

Investigations[9]

Blood tests

- U&Es - concurrent low sodium suggests thiazide use or marked volume depletion.
- Serum bicarbonate.

- Serum glucose.
- Serum chloride.
- Serum magnesium - low serum magnesium often accompanies hypokalaemia and needs to be corrected to enable recovery of serum potassium.
- Spurious - potassium is taken up by cells outside the body - eg, white cells in leukaemia; especially likely to occur if there are delays in analysing the sample.[9]

ECG[10]

All patients with moderate or severe hypokalaemia should have an ECG to determine whether the hypokalaemia is affecting cardiac function and/or to detect digoxin toxicity. Mild hypokalaemia in high-risk individuals should also prompt an ECG, particularly if of recent onset.

Typical ECG findings when potassium is <3.0 mmol/L[11]

- Flat T waves.
- ST depression.
- Prominent U waves.

NB: the QT interval may appear prolonged but this is usually a pseudo-prolongation as the flattened T waves merge into the U waves.

Ventricular arrhythmias such as premature ventricular contractions, torsades de pointes, ventricular tachycardia and ventricular fibrillation can also occur.[12]

Urine tests

- Urinary potassium - where low, suggests poor intake, shift into the intracellular space, or GI loss. Where high, suggests renal loss.
- Urinary sodium - low urinary sodium combined with high urinary potassium suggests secondary hypoaldosteronism.
- Urinary osmolality - needed to interpret urinary potassium levels.

Additional tests

These will be directed towards the underlying cause of hypokalaemia or associated problems and may include:

- Serum magnesium, calcium, phosphate.
- Serum digoxin.
- Arterial blood gases (to establish metabolic acidosis/alkalosis).
- Urinary calcium excretion (if Bartter's syndrome is suspected).
- Serum renin, aldosterone, and cortisol.
- 24-hour urine metanephrines, sodium and potassium.
- Low-dose dexamethasone suppression test or dexamethasone corticotropin-releasing hormone test (if Cushing's syndrome is suspected).
- Pituitary imaging (to evaluate Cushing's syndrome).
- CT scan of adrenal glands.
- Renal angiogram (to exclude renal artery stenosis).
- TSH (if hypokalaemic periodic paralysis is suspected).
- Sweat chloride test (for cystic fibrosis).

Hypokalaemia treatment and management [1] [13]

Multiple observational studies suggest that the optimal range for potassium is 4-5 mmol/L.[2] The management of hypokalaemia is almost always by potassium replacement. The amount of supplementation required depends on the severity of the hypokalaemia. Urgency of replacement is also guided by severity and other medical problems (eg, recent myocardial infarction, digoxin use).

Primary care [14]

A blood result indicating hypokalaemia is a reasonably common problem in general practice. Assess its urgency based on:

- Severity of hypokalaemia.

- Rate of change since previous sample (falls are of increasing significance as they approach 0.5 mmol/L; smaller changes may result from statistical variation).
- Existence of risk factors for arrhythmias (elderly, heart disease, digoxin).
- Risk of ongoing losses (eg, continuing diarrhoea).

Spurious hypokalaemia may occur where unseparated blood has been stored at high, ambient temperatures - for example, during hot weather.

Where potassium is ≤2.5 mmol/L in any patient

- Compare with previous results - if inconsistent, repeat urgently.
- Perform an ECG.
- Discuss with the medical team: admission is usually indicated.
- Consider first aid where a critical ECG emerges.

. **Where potassium is between 2.5-3.0 mmol/L in any patient**

- Compare with previous results - if inconsistent, repeat on same/next-day basis.
- Assess clinical status and risk.
- Perform an ECG.
- Seek urgent advice where there are symptoms or an at-risk patient.
- Consider risks/benefits of ambulatory potassium replacement on an individual basis.

Where potassium is between 3.1-3.5 mmol/L

- Compare with previous results.
- Repeat, with creatinine, sodium and bicarbonate.
- In otherwise untreated, low-risk individuals, hypokalaemia in this range may be of limited clinical significance.
- Ambulatory replacement where indicated.

Oral ambulatory treatment

This is appropriate for mild hypokalaemia and low-risk moderate hypokalaemia and consists of:

- Treating the underlying cause.
- The use of dietary supplementation.
- Potassium supplementation of between 40-120 mmol/day, depending on severity.
- Regular monitoring - weekly to several times weekly, depending on severity.
- Targeting replacement to 4.5 mmol/L or more in higher-risk patients (but beware renal insufficiency).

Oral potassium replacement is generally preferable to supplementation. Potassium-rich foods famously include bananas (one medium banana contains 12 mmol potassium) but other fruit and vegetables are also high in potassium - eg, tomatoes (tomato juice contains 8 mmol/100 ml glass), avocados, potatoes, mangoes and apricots.[15] Dietary manipulation has been shown to be as effective as the use of oral potassium replacement in the prevention of hypokalaemia in postoperative cardiac patients receiving diuretics.[16]

Potassium supplements are usually given as potassium chloride (KCl) in divided doses of between 40-120 mmol/day. Modified-release formulations have been associated with cases of gastric erosions so the British National Formulary (BNF) recommends liquid-based (Kay-Cee-L®) or effervescent preparations (Sando-K®), rather than modified-release preparations (Slow-K®), as first-line. [17]

Potassium phosphate can be used for patients with combined potassium and phosphate depletion (eg, in liver cirrhosis or diabetic ketoacidosis) and potassium bicarbonate is suitable for patients with potassium depletion and metabolic acidosis (eg, distal renal tubular acidosis).

Secondary care

Correction of severe hypokalaemia or hypokalaemia in a high-risk patient should take place in a hospital setting as it is potentially hazardous. Even with severe or symptomatic moderate hypokalaemia, oral potassium replacement may be used if:

- Oral supplements can be taken safely.
- They are likely to correct potassium levels rapidly enough.
- GI function and speed of absorption are adequate.

An oral dose of 20-40 mmol potassium 2-4 times daily is usually enough to correct the deficiency, either in the chloride salt or as bicarbonate or citrate where there is also an acidosis. The patient may also be receiving additional sources of potassium, such as those in IV fluids or in TPN, and these should be included in calculations.

Where oral replacement is not possible, IV replacement is used. *Never* bolus KCl, as it can cause fatal arrhythmias.

- KCl is usually infused via a peripheral line:
    - Give in a normal saline infusion, as dextrose may exacerbate the hypoglycaemia by provoking insulin production.
    - The rate via a peripheral line should not exceed 10 mmol/hour to avoid discomfort and phlebitis.
    - Careful monitoring is required both of clinical condition and bloods (1- to 3-hourly).
    - Once ECG abnormalities, muscle weakness or paralysis are resolving, slow the rate of replacement or switch to oral replacement.
- Higher rates of replacement (>0.25 mmol/kg/hour) can be used in an emergency but require a central line and continuous cardiac monitoring. The maximum rate of replacement should be 0.5 mmol/kg/hour with weight capped at 80 kg (eg, 40 mmol/hour in an 80 kg adult).

Psychiatric referral is required, in addition to medical treatment, if hypokalaemia is the initial presentation of anorexia or bulimia nervosa.

Complications

There is evidence that hypokalaemia is an independent marker for worse outcomes, in low-risk patients attending emergency departments.[18]

- Cardiac arrhythmias and sudden cardiac death[19] (those with congestive cardiac failure, underlying coronary heart disease, and on digoxin or aggressive therapy for hyperglycaemia in diabetic ketoacidosis are most vulnerable).
- Muscle weakness, flaccid paralysis, rhabdomyolysis.[20]
- Abnormal renal function including nephrogenic diabetes insipidus, metabolic alkalosis (due to enhanced bicarbonate absorption) and enhanced renal chloride excretion.
- Iatrogenic hyperkalaemia.
- Contributes to digoxin toxicity.
- Contributes to the development of hepatic encephalopathy in cirrhosis.

Prevention

It is seldom necessary to use potassium supplementation with low-dose diuretics used as antihypertensives. However, individuals on higher-dose diuretic treatment are likely to require preventative measures:

- Where possible, the use of potassium-sparing diuretics (eg, spironolactone, amiloride) is preferable to oral potassium supplements for those on potassium-lowering diuretics.
- Avoid the use of a potassium-sparing diuretic and potassium supplements.
- Where potassium salts are used to prevent hypokalaemia, approximately 25-50 mmol/day in divided oral doses is usual. Smaller doses should be used if there is danger of renal insufficiency, especially in the elderly. Potassium salts can cause nausea and vomiting, so poor concordance is common.
- Long-term oral potassium supplementation requires careful monitoring.

Further reading

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